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which is believed to assist its secretion through various cell membranes as well as a membrane-binding domain (usually hydrophobic in nature and occurring at the C-terminal end) which is thought to preclude its complete secretion through the cell membrane. As such, it remains functionally associated or bound to the membrane. This invention is particularly directed to the exploitation of those membrane-bound polypeptides associated with pathogenic organisms, e.g., herpes virus. The polypeptides of the invention are capable of raising neutralizing antibodies against in vivo challenge by a pathogen.

In accordance with 37 CFR § 1.121, a marked up version of the above-amended paragraph(s) illustrating the changes introduced by the forgoing amendment(s) is provided in Appendix B.

REMARKS

Status of the Claims.

Claims 10-23 and 25-41 are pending with entry of this amendment. Applicants note that the Office Action Summary indicates that claims 1-23 and 25-41 are pending but believe that claims 1-9 were included in error. For the Examiner's convenience, a copy of the pending claims is attached as Appendix A.

Objections to the Specification.

The Examiner objected to the specification on the ground that the specification allegedly "does not provide proper antecedent basis for the phrase "capable of raising neutralizing antibodies." Office Action, page 3. Applicants note that the specification contains ample support for this phrase. *See, e.g.*, page 2, lines 7-14 (discussing the ability of a truncated form of a normally membrane-bound protein "to raise antibodies effective against the pathogen from which the protein is derived); page 3, lines 1-4 (using the term "virus neutralization); page 4, lines 21-31 (describing that one embodiment of the invention concerns expressing a truncated form of the herpes gD protein that "could raise antibodies effective against HSV-1 and/or HSV-2;" and page 28, line 16 to page 31, line 33 (describing in vivo virus challenge studies using the polypeptides of the invention).

In addition, the specification has been amended to add a sentence containing the phrase "capable of raising neutralizing antibodies" to the Summary of the Invention. (The support

for this amendment is as discussed above and therefore the amendment adds no new matter.

Therefore, if the objection is based on the Examiner's belief that this phrase should appear *ipsis verbis* in the specification, the objection is now moot.

The Examiner also objected that that term "immunogenic composition" allegedly does not have proper antecedent basis in the specification. Office Action, page 3. The Examiner does acknowledge, however, that the specification provides antecedent basis for the term "vaccine." *Id.* Applicants respectfully point out that the specification describes the invention as follows:

The success of this invention in demonstrating that a truncated form of a membrane bound protein, lacking that part of hydrophobic-hydrophilic carboxy-terminal region responsible for binding it to the membrane, can yet be *immunogenic* indicates that similar results can be expected with other immunogenic membrane bound proteins

Applicants' specification, page 34, lines 4-10 (emphasis added). Applicants submit that this passage clearly describes the truncated form of the membrane bound-protein as an immunogenic composition, thus providing proper antecedent basis for the preamble of the pending claims. Withdrawal of the objection is therefore respectfully requested. If the Examiner still maintains that the antecedent basis in the specification is insufficient, Applicants are willing to amend the specification to insert the term "immunogenic composition."

Applicants note the Examiner's statement that "the term 'vaccine' . . . is known to be an immunogenic composition with a very narrow meaning in that it requires a prophylactic effect." Office Action, page 3. However, the Examiners' statement overlooks the fact that vaccines can be either prophylactic (*i.e.*, protective) or therapeutic and that the specification discusses both types of vaccines. *See* Applicants' specification, page 4, line 35- page 5, line 3. An important feature of any type of vaccine is its ability to raise neutralizing antibodies against the pathogen. This feature is included in all pending claims.

35 U.S.C. § 112, First Paragraph.

Claims 10, 32, 40, and 41 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that the specification allegedly "does not reasonably provide enablement for using any truncated glycoprotein as an immunogen to elicit neutralizing antibodies . . . that would be effective

at protecting the animal from challenge by the pathogen.” Office Action, page 3. Applicants respectfully traverse.

The Examiner notes that the “claims would include truncated HIV glycoproteins.” *Id.* at page 4. The Examiner therefore cites Yang *et al.* (Journal of Virology 2001) as evidence that “[m]ost recombinant HIV-1 glycoproteins have been monomers . . . of gp120 . . . [and] the elicitation of neutralizing antibodies has been weak.” *Id.* According to the Examiner:

Yang et al. show the production of soluble trimers of HIV-1 in which the transmembrane (membrane binding domain) has been deleted and is effective for raising neutralizing antibodies. The reference indicates that there are definite structural requirement[s] for the epitopes to obtain a good immune response. . . . The reference indicates that each antigen must be tested for its ability to raise a neutralizing immune response and that this cannot be predicted from the structure alone, should the structure even be known.

Office Action, page 4.

Applicants respectfully submit that Yang does not establish that undue experimentation would be required to practice the claimed invention using an HIV gp120 polypeptide. In particular, claim 10 relates to a “truncated, membrane-free derivative” of a polypeptide that, in its native form, comprises a membrane-binding domain. The native form also comprises antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen. As recited in claim 10, the truncated derivative “has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen.” Yang does not, as the Examiner appears to believe, teach that HIV gp120 is not capable of raising neutralizing antibodies against in vivo challenge. To the contrary, Yang explicitly states: “To date, no defined immunogen has proven better than the gp120 glycoprotein, which generates primary virus-neutralizing activity only after an aggressive immunization protocol involving many boosts.” Yang, page 1167, col. 1. This statement clearly indicates that the gp120 glycoprotein “has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen.” Yang states “that soluble, stabilized trimers [of gp120] are more effective than gp120 at eliciting antibodies that neutralize HIV-1.” *Id.* Thus, while Yang has perhaps improved the neutralizing antibody response, the fact remains that the gp120 monomer does, in fact, elicit a neutralizing antibody response. Because Yang indicates that the claimed invention can be practiced

using an HIV gp120 polypeptide, Yang supports Applicants' position that the specification fully enables the claims.

In justifying the enablement rejection, the Examiner also relies on Paul (Fundamental Immunology, Raven Press, New York, NY; 1993, 3rd edition). The Examiner notes that, at page 251, column 1, lines 11-12, Paul "states that immunogenicity is limited by self-tolerance, and that the repertoire of potential antigenic sites in a given polypeptide is specific for the host organism." Office Action, page 4. In the passage cited by the Examiner, Paul explains that a host organism will produce antibodies specific for antigenic sites in an immunogenic polypeptide that are not shared with host polypeptides. Thus, Paul states that "sheep antibodies bound beef but not sheep myoglobin, even though these two myoglobins differ by just six amino acids." Paul, page 251, col. 1.

Applicants respectfully submit that the phenomenon of self-tolerance has no bearing on the enablement of claim 10. More specifically, claim 10 recites a truncated derivative of a normally membrane-bound polypeptide that includes "antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen." Thus, to practice claim 10, one skilled in the art can simply identify a native polypeptide that includes a membrane-binding domain and also includes such antigenic determinants. The passage relied on by the Examiner does not suggest that this would be difficult, given that, as exemplified in the application, a pathogen polypeptide could be selected for this purpose. See Applicants' specification, page 8, line 27 to page 34, line 24. Most pathogen polypeptides would be expected to have significantly different amino acid sequences from those found in the corresponding host organisms. Upon immunization, any antigenic determinants common to the host and pathogen polypeptides would be, as Paul says, "screened out" by the host immune system, which would produce antibodies to non-shared antigenic determinants in the pathogen polypeptide. See Paul, page 251, col. 1. Thus, the passage on page 251 of the Paul reference says nothing about the amount of experimentation required to achieve the immune response recited in claim 10.

The Examiner also relies on Paul for the notion "that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody." Office Action, pages 4-5 (citing Paul, page 249, col. 2, lines 10-13). This passage on page 249 of

the Paul reference concerns one of the features of protein structure that correlates with immunogenicity, namely surface accessibility. However, this passages does not, in any way suggest, that structural information is required to determine the presence of neutralizing epitopes in a given polypeptide.

Rather than attempting to predict the presence of neutralizing epitopes based on protein structure, one skilled in the art can simply follow the teachings of the specification and test the ability of a native polypeptide and/or a truncated form thereof to raise neutralizing antibodies against in vivo challenge by a pathogen. Examples of such studies are described in detail in the specification, for example, at page 27, line 11 through page 29, line 20 (HSV-1 virus challenge study) and at page 30, line 14 through page 31, line 33 (HSV-2 virus challenge study). Thus, Applicants submit that Paul's teaching that structural information is needed to determine the surface accessibility of a protein region is irrelevant to the enablement of claim 10.

In summary, Yang indicates that claim 10 is enabled with respect to HIV gp120, and Paul is irrelevant to the issue of whether one skilled in the art could practice the invention without undue experimentation. Thus, the evidence cited by the Examiner in support of the enablement rejection is insufficient to establish a *prima facie* case of non-enablement. Rejected claim 32 recites a nucleic acid encoding the truncated, membrane-free derivative of the composition recited in claim 10. Rejected claims 40 and 41 recite specific embodiments of the composition recited in claim 10 in which the pathogen is a virus. For the same reasons as discussed above with respect to claim 10, Applicants submit that the Examiner has failed to establish a *prima facie* case of non-enablement with respect to any these rejected claims. Withdrawal of the rejection is therefore respectfully requested.

Obviousness-Type Double Patenting.

Claims 10-12, 14-19, 25-29, and 32-41 were rejected for obviousness-type double patenting over claims 13, 19, and 20 of U.S. Patent No. 4,855,224. Office Action, page 5. The rejection is respectfully traversed.

The Examiner stated that the "patented claims are drawn to diagnostic products, which have the same structure as the instantly claimed immunogenic composition." Office Action, page 6. However, Applicants submit that the pending claims recite at least one structural-functional element that clearly distinguishes the claims of the '224 patent. Specifically, the pending claims

recite "a truncated, membrane-free derivative of a polypeptide . . . [that] has exposed antigenic determinants capable of raising neutralizing antibodies against *in vivo* challenge by the pathogen." See claim 10. By contrast, the claims of the '224 patent relate to diagnostic kits comprising polypeptides "capable of specifically binding complementary antibodies." See claim 13. Because the claims of the '224 patent relate to diagnostics, the recited polypeptides need only be capable of binding complementary antibodies. The antibodies bound need not be neutralizing antibodies. That it is possible to produce a truncated, membrane-free derivative of a polypeptide that retains the ability to *bind* complementary antibodies suggests nothing regarding the possibility of producing a truncated, membrane-free derivative that has the ability to *raise neutralizing* antibodies *in vivo*. This difference in the requirements for how the truncated polypeptide functions reflect different structural requirements because, as the Examiner has pointed out, "[c]hemical compounds and their functions are inseparable." Office Action, page 7. Thus, the claims of the present application incorporate a structural-functional requirement that is not suggested by the claims of the '224 patent. Because the pending claims are not obvious variants of any of the claims of the '224 patent, Applicants respectfully request withdrawal of the obviousness-type double patenting rejection of claims 10-12, 14-19, 25-29, and 32-41.

Claims 10-23 and 25-41 were also rejected for obviousness-type double patenting over claims 13, 19, and 20 of the '224 patent in view of Watson *et al.* (Science 1992) and Dundarov *et al.* (Dev Biol Stand. 1982). Office Action, page 7. (Claim 24 was also rejected on this ground, but this rejection is moot, as claim 24 was previously cancelled.) This rejection is respectfully traversed. As noted above, the claims of the '224 patent fail to suggest a truncated, membrane-free derivative that has the ability to *raise neutralizing* antibodies *in vivo*. Neither of the secondary references remedy this deficiency.

Watson is cited merely for the proposition that "following the procedure provided in the patent would result in the production of [an] HSV gB immunogenic composition that would produce neutralizing antibodies to HSV gB". Office Action, page 8. Applicants respectfully point out that the proper focus of a double patenting issue is on the claims of the reference patent, not the entire patent specification. As claims 13, 19, and 20 are all composition claims, Applicants submit that any reliance on "the procedure provided in the patent" is improper.

In addition, the Examiner's attention is directed to the Declaration Under 37 C.F.R. § 1.131 filed previously in this case with an Amendment dated February 5, 1997. The Amendment stated:

Applicants asserted, and assert herein, that the enclosed Declaration under 37 C.F.R. § 1.131 is fully sufficient to remove the various references cited herein, namely, Watson (and related Watson references referred to as "collective Watson references" discussed in detail below) as well as Rose Kaufman and Chan. Thus, the rejections must and do fall.

Feb. 5, 1997 Amendment. At page 14, the Feb. 5 Amendment refers to the Watson *Science* article, which is believed to be the same Watson reference cited in the double patenting rejection.

Applicants cannot be sure of this, however, as the Examiner has indicated that the Watson reference was published in 1992, which appears to be a typographical error. If the Examiner continues to rely on the cited Watson reference, the Examiner is requested to provide the full citation and state why, in light of the previously filed § 1.131 Declaration, Watson is considered to be a proper reference against the present application.

Dundarov is cited as teaching the "use of polyvalent HSV vaccine for producing an immune response [*sic*] in a host." Office Action, pages 8-9. The Examiner contends that this teaching, in combination with those of claims 13, 19, and 20 of the '224 patent and Watson, suggests the claimed immunogenic compositions comprising combinations of HSV glycoprotein derivatives. *See, e.g.*, claim 21. Dundarov describes the use of inactivated polyvalent herpes vaccines. These studies teach or suggest nothing regarding a truncated, membrane-free derivative that has the ability to *raise neutralizing* antibodies *in vivo*. Thus, the claims of the present application incorporate a structural-functional requirement that is not suggested by the claims of the '224 patent taken, alone or in any combination, with Watson and/or Dundarov. Applicants therefore respectfully request withdrawal of the obviousness-type double patenting rejection of claims 10-23 and 25-41.

Claims 10, 11, 14-19 and 32-41 were rejected for obviousness-type double patenting over claims 1-10 of U.S. Patent No. 5,851,533. Office Action, page 9. In addition, claims 10-23 and 24-41 were rejected for obviousness-type double patenting over the '533 patent in view of Watson *et al.* (*Science* 1992) and Dundarov *et al.* (*Dev Biol Stand.* 1982). *Id.* at page 10. (The Examiner's rejection of claims 1-41 is believed to be a typographical error, as claims 1-10 and 24 are not

pending in the application.) Applicants will consider filing a terminal disclaimer to obviate these rejections upon receiving an indication that the claims are otherwise allowable.

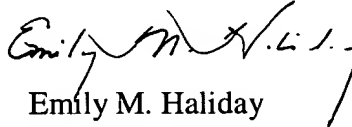
Conclusion

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

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